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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/554,602	07/14/2000	CORINNE DEGERT	00108	8317

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EXAMINER

KISHORE, GOLLAMUDI S

ART UNIT	PAPER NUMBER
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1615

DATE MAILED: 05/14/2003

18

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/554,602

Applicant(s)

Degert

Examiner

Gollamudi Kishore

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Feb 14, 2003
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 22-41 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 22-41 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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DETAILED ACTION

The request for the extension of time and amendment dated 2-14-03 are acknowledged.

Claims included in the prosecution are 22-41.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 22-34 and 40-41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of U.S. Patent No. 5,908,697. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant generic 'surfactant' includes the specific surfactant recited in the claims of said patent.

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Applicant's arguments have been fully considered, but are not found to be persuasive. First of all, it should be pointed out that claim 22 recites the surfactant (claim 25 further limits the surfactant). Applicant argues that presence of surfactant is not relevant and that the claimed surfactant is not a stabilizer for the active. This argument is not found to be persuasive since the examiner did not state that the surfactant is the stabilizer. The claims in 697 patent recite polymers (see claim 12) which include both synthetic and natural polymers such as gelatin (a polyamide) and polysaccharides and instant claim 38 lists these polymers as stabilizers. Irrespective of their function, the claims in both the patent and instant application recite the same compositions with obvious changes.

3. Claims 22-34 and 40-41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 12 of U.S. Patent No. 6,277,404. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant generic liposomes encompass the liposomes recited with size ranges in the claims of said patent.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant once again argues that there is no suggestion in the cited patents to incorporate in the vesicles an active compound together with a compound for inhibiting the degradation of the active compound. This argument is not found to be persuasive since as stated before (and above) although the disclosures in said patents do not specifically state

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that the polymers and polysaccharides recited as 'stabilizers' the claims in the patents recite the active agents and the same polymers and polysaccharides.

The rejections are maintained.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 22-28, 32-34 and 40-41 are rejected under 35 U.S.C. 102(b) as being anticipated by CA 2133421 of record.

The Canadian patent discloses multi lamellar vesicles containing stacked bilayers and made from both ionic and non-ionic surfactants. The vesicles contain either hydrophobic or hydrophilic active agents and also contain a polymer (polyacrylamide) (note page 2, line 12 through page 3, line 11, page 7, Examples and claims).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant while agreeing that the Canadian reference is directed to vesicles of the same type as those presently claimed, once again argues that the stabilization of the structure of the vesicles by reinforcing their rigidity with a polymer and that this is purely

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a physical effect and that there is no disclosure or suggestion of stabilizing the active substance which is incorporated in the vesicles by incorporation of a stabilizing agent. This argument is not found to be persuasive; the examiner once again points out that the rejected claims are composition claims and the reference teaches the same polymers as in instant claims (see the paragraph bridging pages 2 and 3 and instant claims 37 and 38).

6. Claims 22-31, 33-34 and 40-41 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/31194 of record.

WO discloses multi lamellar non-phospholipid liposomes containing surfactants, retinol, tocopherol, vitamin C and other antioxidants (note the abstract, pages 9, 10, 13 and examples, Examples 7 and 8 in particular).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant pointing out the figure 1, once again argues that the reference teaches classical multi lamellar liposomes containing an interior medium, whereas the liposomes of the invention include an aqueous medium which alternates continuously with the lipophilic medium. In response to the examiner's position that instant claims do not distinguish over the prior art, applicant argues that the claims have been amended and the amendment reciting "the regular stack of concentric bilayers" distinguishes the instant product from the prior art. It is unclear how this amendment distinguishes instant product from prior art since the specification on page 6, lines 7-9 recites the same limitation for multilamellar vesicles. According to applicant at this location, "Onion-structure

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multilamellar vesicles are in the form of *regular stack of concentric bi-layers going from the very core of the vesicle to the periphery*". As pointed out in the previous actions, While it is understandable that instant vesicles are different from multi lamellar vesicles, the instant claim language does not distinguish instant product over the prior art multilamellar vesicles.

- 7. Claims 22-27 and 33-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Munechika (5,662,931).**

Munechika discloses multi lamellar liposomes containing lecithin, a surfactant and enzymes such as urokinase. The liposomes further contain, stearylamine and cholesterol; the liposomes also contain proteins and polysaccharides as stabilizers (note the abstract, columns 2-3, Examples).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments that Munechika's are classical liposomes are similar those put forward for the rejection of claims over WO 96/31194 reference and hence the same response is applicable. Applicant's arguments (based on Muhechika's citing of a JP references as prior art) that in Munechika, the degradation of active agent is during the preparation and that there is no disclosure of inhibiting degradation of the active after the formation of the resulting liposomes are not persuasive since according to col. 3, lines 8-11, the proteins and polysaccharides are present in the composition as stabilizers. Applicant

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argues that it appears from col. 2, line 60 et seq., that tocopherol is used to stabilize the lipid and not the active agent. This argument is not found to be persuasive since tocopherol is a known anti-oxidant and it would prevent the oxidation of the active agent irrespective of the nature of the active agent which is prone to oxidation (see page 14 of instant specification which recites the same principle). Secondly, by stabilizing the lipid making up the bilayer and thereby making the bilayer membrane leak-proof, the tocopherol indirectly prevents the active agent from chemical degradation by external factors outside the liposomes and instant claim language does not exclude this indirect stabilization.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. Claims 22-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over CA 2133421 or WO 95/18601 in view of Munechika (5,662,931) cited above.

As pointed out above, the Canadian patent discloses multilamellar vesicles containing stacked bilayers and made from both ionic and non-ionic surfactants. The vesicles contain either hydrophobic or hydrophilic active agents and also contain a polymer

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(polyacrylamide) (note page 2, line 12 through page 3, line 11, page 7, Examples and claims). What is lacking in CA is an explicit teachings of including a stabilizer for the hydrophilic drug or enzyme along with the drug or enzyme. CA also lacks a specific teaching of the hydrophilic drug to be an enzyme.

As pointed out above, WO 95 discloses multi lamellar liposomes, a method of preparation forming first a lamellar liquid crystalline phase and adding water. The active agents include vitamins, hydroxy acids and others (note the abstract, page 5, examples, Example 10 in particular). What is lacking in WO is an explicit teachings of including a stabilizer for the hydrophilic drug or enzyme along with the drug or enzyme. WO also lacks a specific teaching of the hydrophilic drug to be an enzyme.

Munechika discloses multi lamellar liposomes containing lecithin, a surfactant and enzymes such as urokinase. The liposomes further contain, stearylamine, cholesterol and an antioxidant. Munechika also discloses the incorporation of polymers such as albumin, dextran, gelatin and others as stabilizers (note the abstract, columns 2-3, Examples).

Encapsulation of a stabilizer such as albumin, gelatin or a polysaccharide along with a drug in the multi lamellar vesicles of CA or WO would have been obvious to one of ordinary skill in the art since Munechika teaches that these polymers stabilize the drugs such as urokinase.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments with regard to CA and WO have been fully addressed

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above. Applicant's arguments that Munechika does not cure the deficiencies of the primary references since cholesterol, dextran, gelatin and albumin are not chemical stabilizers are not persuasive: the reason being that contrary to applicant's arguments, the reference of De Rosier cited of interest before, clearly teaches that albumin is a known stabilizer for enzymes. Applicant argues that the examiner's assertion that albumin is a known enzyme stabilizer is not completely correct since the teaching of DeRosier is that it is necessary to combine a polysaccharide with a protein (albumin) to obtain a stabilizing effect. This argument is not persuasive since the examiner cited this reference to show the stabilizing effect of albumin on enzymes whether it is in combination or by itself. Albumin by itself is well known to stabilize to enzymes. The examiner cites the following as interest.

US 5,582,698 which teaches albumin stabilizes glucose oxidase (note col. 15, lines 35-36);

US 5,516,647 which teaches that albumin stabilizes alkaline phosphatase (note col. 23, lines 18-20);

US 5,075,216 which teaches that gelatin stabilizes DNA polymerase (note col. 7, lines 37 and 38);

US 4,495,285 which teaches that albumin stabilizes urokinase (col. 1, lines 55-56);

US 4,366,243 which teaches that albumin stabilizes glutathione synthetase (note col. 3, lines 14-17);

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10. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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- 11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.**

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

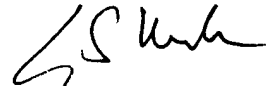
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.



Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600

gsk

May 12, 2003